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Assessment report for diacerein containing medicinal products

Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

INN: diacerein

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Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.



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1. Background information on the procedure

On 22 November 2012, further to the evaluation of data resulting from pharmacovigilance activities, France informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their consideration that, in view of the safety profile of diacerein containing medical products (very frequent digestive disorders, skin reactions sometimes serious, hepatic disorders more often cytolytic with one fatal case and some serious cases reported) and taking into account evidence from clinical trials and the scientific literature suggesting that the effectiveness of diacerein in osteoarthritis was weak, the benefit-risk balance of diacerein containing medicinal products in the symptomatic treatment of osteoarthritis of the hip and knee might become unfavourable and therefore it was in the interest of the Union to refer the matter to the PRAC for assessment.

The French competent authority (Agence nationale de sécurité du médicament et des produits de santé, ANSM) therefore requested the PRAC to give a recommendation on the balance of benefits and risks of diacerein containing medicinal products in the authorised indications and to conclude on whether relevant marketing authorisations should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

Diacerein is a symptomatic slow acting drug in osteoarthritis (SYSADOA). Even though its mechanism of action is not completely known, it differs from non-steroidal anti-inflammatory drugs (NSAIDs) as it does not inhibit prostaglandin synthesis nor affect its levels. Diacerein and its active metabolite, rhein, are anthraquinone derivatives. It is thought that diacerein works by blocking/reducing the actions of interleukin-1 β , a protein involved in the process of articular cartilage destruction and synovial inflammation (*Yaron M et al., 1999; Alvarez Soria et al., 2008; Legendre F et al., 2009*).

Diacerein is mainly indicated as an oral treatment for osteoarthritis (OA), a chronic joint degenerative disease with a high prevalence in the ageing population. The prevalence of symptomatic knee OA in patients aged 35-54 years is around 1%, whereas about 40% of the population aged over 65 has symptomatic OA of the knee or hip. OA of the knee is more prevalent than hip OA.

Pain and functional disability of the affected joints are the main manifestations of osteoarthritis. The correct diagnosis includes both clinical and radiological criteria.

In general, treatment includes non-pharmacological therapies such as weight control, physical therapy, exercise, patient education as well as pharmacological intervention. An acute flare of OA is usually treated with analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) or an intra-articular injection with corticosteroids for fast symptom relief. Topical NSAIDs are also used for knee OA. For non-acute treatment, symptomatic slow acting drugs for OA (SYSADOA) are available. SYSADOAs in use in different Member States include glucosamine, chondroitin sulphate and diacerein. Some nutraceuticals are usually also included in this group.

There is no consensus on the role of SYSADOA in the pharmacological treatment of OA. In general its place in therapy is considered supplementary to the analgesics and anti-inflammatory drugs.

Diacerein is currently authorised through national procedures in the following EU Member States: Austria, Czech Republic, France, Greece, Italy, Portugal, Slovakia and Spain.

In 2012, the ANSM initiated a review of the benefit-risk of diacerein containing medicinal products that underlined the occurrence of very frequent digestive disorders, cases of hepatitis and serious skin reactions in patients treated with diacerein. In addition, and according to the clinical trials and bibliographical data, the efficacy appeared weak in the symptomatic treatment of osteoarthritis with low impact on pain and functional symptoms and with no demonstration of a decrease of NSAIDs

intake in the population treated with diacerein. The French competent authority considered that the benefit-risk balance of diacerein had become unfavourable in the symptomatic treatment of osteoarthritis of the knee and the hip and that the marketing authorisations should not be maintained.

In view of the above, the ANSM requested the PRAC to give a recommendation on the balance of benefits and risks of diacerein containing medicinal products in the authorised indications and on whether their marketing authorisations should be maintained, varied, suspended or withdrawn.

2.1. Clinical Efficacy

Diacerein is mainly indicated as an oral treatment for degenerative joint diseases (osteoarthritis). It is taken by oral route and the recommended daily dose is 50 mg twice a day. Its action onset is slow, beginning towards day 30 of treatment.

As specified in the guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis (CPMP/EWP/784/97 Rev.1, January 2010) regarding medicinal products intended to improve symptoms of osteoarthritis, pain is regarded as one of the main osteoarthritis (OA) related symptoms.

The effects of diacerein on pain have been evaluated using visual analogue scale (VAS) as well as the Western Ontario and McMaster Universities Arthritis Index (WOMAC), a set of standardised questionnaires used to evaluate the condition of patients with osteoarthritis of the knee (KOA) and hip (HOA), including pain (WOMAC A, five items), stiffness (WOMAC B, two items), and physical functioning (WOMAC C, 17 items) of the joints, and the Lequesne Index, which was developed to assess the severity for osteoarthritis for the knee (ISK). The Lequesne Index includes the measurement of pain (five questions), walking distance (one question), and activities of daily living (four questions), with versions available for the hip and knee. The structure-modifying effects of diacerein have also been assessed as primary endpoint in few studies as well as its NSAIDs sparing effect (secondary endpoint).

The data from a number of non-clinical studies, randomised clinical trials, epidemiology studies and meta-analysis have been considered during this referral procedure. Only the most relevant data are summarised in this report.

2.1.1. Randomised controlled clinical trials

2.1.1.1. Effect on pain and physical functioning

The below table provide a summary of the published double-blind randomised controlled clinical trials with diacerein in the treatment of osteoarthritis of the hip and knee and of their efficacy results for pain or physical functioning.

Reference (year)	OA site	Control	Nr. randomised diacerein /control	Treatment assessment/ Post - treatment assessment	Type of analysis	Primary end point/secondary end points	NSAIDs use	Efficacy (diacerein (DR) vs control)
Amor & Dougados (Nguyen et al.,1994)	Hip	Placebo (factorial design)	75/71	2 months No	ITT	Pain 100mm VAS abs change from baseline	No	-29mm DR -20mm pcbo (p=0.025)
Amor & Dougados (Nguyen et al.,1994)	Hip	Tenoxicam 20mg/day (factorial design)	75/75	2 months No	ITT	Pain 100mm VAS abs change from baseline	No (tenoxicam controlled)	-29mm DR - 29mm Tenox (NS)
Amor & Dougados (Nguyen et al.,1994)	Hip	Placebo (factorial design)	67/71	2 months No	ITT	Pain 100mm VAS abs change from baseline	Tenoxicam2 0mg/day	-32mm DR + tenox -20mm pcbo (p=0.025)
Ascherl (1994)	Knee	Placebo	59/54	6 months No	ITT 59/52	Function disability (Lequesne index), change from baseline	No	-4.53 DR -2.80 pcbo (p=0.0138)
Schulitz (1994)	Knee	Placebo	40/40	3months No	PP 26/30	Function disability Lequesne index, change from baseline	No?	-8.5 DR -11 pcbo (p<0.05)
Schulitz (1994)	Knee	Placebo	40/40	3months No	PP 26/30	Pain 10cm VAS abs change from baseline	No?	-4.8 DR -5.5 pcbo (NS)
Lequesne (1998)	Hip/ knee	Placebo	90/93	6 months 8 months	IT	Pain 100mm VAS abs change from baseline	0-2m: Diclofenac 100mg/day 2-8m: permitted	6 months: -- - 20.1mm DR -9.0mm pcbo (p<0.0046 8 months_ -22.2mm DR -11.6mm pcbo (p<0.0069)
Pelletier (2000)	Knee	Placebo	111/125	4 months No	ITT 110/124	Pain 100mm VAS abs change from baseline	No	-18.3mm DR -10.9mm pcbo (p<0.05)
Dougados (2001) (ECHODIAH)	Hip	Placebo	255/252	36 months No	Modified ITT 246/247	Pain 100mm VAS abs change from baseline	As rescue	-3mm DR -3mm pcbo (NS)
Pavelka (2007)	Knee	Placebo	84/84	3 months 6 months	Modified ITT 82/83	Pain (WOMAC A) abs change from baseline	No	3 months: -21.6mm DR -9.4mm pcbo (p<0.0001) 6 months: -22.5mm DR -9.3mm pcbo (p<0.0001)
Goupille&Valat (2011)	Knee	Placebo	251/226	3 months No	Modified ITT 231/219	WOMAC A.1.1 score (pain in walking) abs change from baseline	Not provided	-24.2 mm DR -20.3 mm pcbo (NS)
Tang (Zheng et al., 2006)	Knee	Diclofenac 75mg/day	112/111	3 months 4 months	106/107	Pain in walking 20 m (100-mm VAS)	No	3months: NS 4 months: -29.7 DR vs -33.0 diclof (p<0.05)*

Reference (year)	OA site	Control	Nr. randomised diacerein /control	Treatment assessment/ Post - treatment assessment	Type of analysis	Primary end point/secondary end points	NSAIDs use	Efficacy (diacerein (DR) vs control)
Louthrenoo (2007).	Knee	Piroxicam 20mg/day	86/85	4 months 6 months	Modified ITT 82/79	Pain (WOMAC A)	No	NS during treatment Follow-up period: Month 5: 90 vs 145 (p<0.006) Month6: 83 vs 201 (p<0.0001)
Singh (2012)	Knee	Placebo	74	3 months 4 months	Not provided	Pain (VAS) from baseline	Diclofenac 75 mg/day mandatory first 3 months; paracetamol as rescue after	Month 4: -63.50mm DR -47,66mm Pcbo (p = 0.0008)
Pham (2004)	Knee	Placebo	85/85	12 months No	ITT	Symptoms (pain, function) and structural efficacy (JSN)	As rescue (and 3 courses of intra-articular hyaluronic acid)	No differences in any end-point

DR: diacerein; Pcbo: placebo; VAS: Visual Analogue Scale; JSN: Joint space narrowing; NS: non-significant

In nine double blind, randomised clinical trials diacerein has been compared to placebo with regard to pain relief in patients with OA of the knee and/or hip. The Visual Analogue Scale (VAS) was used as end-point. This is generally accepted for products intended to improve symptoms, as is the case for diacerein.

In four of these trials (Dougados, Pham, Schulitz, Goupille and Valat) diacerein was not superior to placebo in the end-point measured as a reduction from baseline on a VAS 0-100mm scale for pain. In other five clinical trials diacerein showed for the same end-point superiority versus placebo. In one of these trials (Pelletier) the effect was of doubtful clinical relevance (absolute reduction of pain in the VAS compared to placebo of less than 8mm on a 100mm scale). In three clinical trials (Lequesne, Pavelka, Singh) diacerein has shown a statistical significant effect versus placebo in the VAS from one to three months after cessation of the treatment with diacerein (carry over effect).

Function disability (Lequesne index) measures have been used as primary end-points in two clinical trials (Ascherl, Schulitz) with statistical significant results in favour of diacerein compared to placebo.

In three clinical trials (Amor & Dougados, Tang, Louthrenoo) effects of diacerein on pain in OA have been compared to NSAIDs (tenoxicam 20mg, diclofenac 75 mg, piroxicam 20 mg daily doses respectively). At the end of treatment no differences between diacerein and NSAIDs were found in the three trials although formal non-inferiority analyses were not performed. In two of these trials, diacerein treated patients showed better results on the pain (VAS) one (diclofenac) and two (piroxicam) months after the end of the study treatments, supporting a carry-over effect of diacerein. However the evidence of the effect of diacerein compared to NSAIDs was limited due to the uncertain clinical relevance of the differences and to the lack of a placebo group in these trials. In addition, in the study by Tang the difference between diacerein and a relatively low dose of diclofenac (75mg/day) could not be considered statistically significant.

2.1.1.2. Impact on radiologic signs

The most relevant study on the impact of diacerein on radiologic signs was the ECHODIAH study (Dougados *et al*, 2001), a randomised, double-blind, placebo-controlled three-year study designed to

evaluate the ability of diacerein to slow the progressive decrease in joint space width observed in patients with hip OA. Five hundred and seven (507) patients with primary OA of the hip received diacerein or placebo. The minimal hip joint space width was measured by a central reader on yearly pelvic radiographs using a 0.1-mm-graduated magnifying glass. The percentage of patients with radiographic progression, defined by a joint space loss of at least 0.5 mm, was significantly lower in patients receiving diacerein than in patients receiving placebo, both in the intent-to-treat analysis and in the completer analysis (50.7% versus 60.4% [$p=0.036$] and 47.3% versus 62.3% [$p=0.007$], respectively). In those patients who completed 3 years of treatment, the rate of joint space narrowing was significantly lower with diacerein (mean + SD 0.18 + 0.25 mm/year versus 0.23 + 0.23 mm/year with placebo; $P = 0.042$). In this study, diacerein had no evident effect on the symptoms of OA (-3 mm on the VAS were observed in each group). However, a post hoc covariate analysis that took into account the use of analgesics and anti-inflammatory drugs showed an effect of diacerein on the Lequesne functional index.

Another study from Pham (2004) was a symptom- and structure-modifying study with diacerein carried out in 301 knee OA patients. This one-year, prospective, multicentre, randomised, double-blind, placebo-controlled, 3-arm study carried out in France, compared two treatments which had a different route of administration. The aim of this study was to evaluate the long-term efficacy of three courses (every three months) of three weekly intra-articular (IA) injections of hyaluronic acid (HA) in the treatment of symptomatic knee OA compared to oral diacerein and placebo. This study assessed symptomatic efficacy (pain, function) and structural efficacy (joint space narrowing, JSN) of both products compared to placebo.

There was a significant improvement from baseline in the three treatment groups. In the diacerein group, the mean change from baseline for VAS pain at one year was -33.9 ± 25.7 mm. However, no statistically significant difference was observed between the different groups ($p = 0.96$). Similarly, no difference was seen in the consumption of analgesics and NSAIDs.

2.1.1.3. NSAIDs sparing effect

No randomised clinical study was performed to assess NSAIDs sparing effect as a primary end point. However data on NSAIDs and/or paracetamol consumption were available in the following studies:

In the Tang study (*Zheng et al., 2006*) no difference in the average paracetamol consumption within four, eight and twelve weeks in the two groups was detected. However, during the follow-up period, the paracetamol consumption (5.83 ± 16.6 tablets) was lower in the diacerein group than in the diclofenac group (21.18 ± 31.12 tablets) ($p<0.001$).

In the Ascherl study (*Ascherl, 1994*), NSAIDs were forbidden all along the study. In the diacerein group, the mean paracetamol consumption per week at baseline was 1.79 tablets, as compared to 2.67 tablets in the placebo group. A decrease in consumption of 46 % and 19 % was observed in the diacerein and placebo group, respectively. However, the consumption of paracetamol was not normally distributed.

In the Schulitz study (*Schulitz et al, 1994*), paracetamol was permitted on the occurrence of severe pain. The use of paracetamol to alleviate pain in the knee was more frequent in the placebo group than in the diacerein group (19 consumptions in the placebo group versus seven in the diacerein group). It was not specified if NSAIDs were forbidden.

In the Lequesne study (*Lequesne et al., 1994*), the total consumption of NSAIDs was significantly lower in the diacerein group (212.7 ± 363.5 mg of equivalent of diclofenac) than in the placebo group (289.8 ± 376.2 mg), between month two and month eight ($p<0,05$) meaning a sparing of 26%. In

addition, the daily consumption of NSAIDs was significantly lower in the diacerein group (1.4 ± 2.4 mg) than in the placebo group (2.2 ± 3.3 mg), between month 2 and month 8: ($p < 0.05$).

In the Pavelka study (*Pavelka et al.* 2007), the daily paracetamol consumption was similar in both groups during the treatment period. However during the follow-up period, it was significantly lower in the diacerein group from month 4, with a mean intake of 1 ± 1.1 tablet/day in the diacerein group versus 1.5 ± 1.4 tablet/day in the placebo group at month 6 ($p = 0.0124$).

In the Goupille and Valat study (*Goupille et al.*, 2001), NSAIDs were forbidden all along the study. There was no difference between groups for paracetamol consumption.

2.1.2. Observational studies

The Pegase study was a post-authorisation study with observational cohort design required in 2009 by the management body of the French healthcare system (Commission de la Transparence, Haute Autorité de Santé, HAS) as a condition for the renewal of the reimbursement of diacerein containing medicinal products (together with other slow action products in OA, or SYSADOA) for medical prescription within the public health care system in France. The primary objective was to study whether treatment with diacerein in knee or hip OA has any impact on the utilisation of NSAIDs.

Patients in general practice and rheumatology clinics in France with symptoms related to OA of knee/hip were recruited for this prospective observational study if they received a new non-pharmacological or pharmacological treatment and consented to participation. The cohort of patients initiating diacerein (424 patients) was compared to patients not exposed to any slow acting symptomatic drug for OA (1258 patients). Eight hundred and twenty-one patients received diacerein at least once.

The statistical analysis was conducted considering two month-periods (named "Time Unity of Analysis" or "TUA"). For each patient, TUA were classified as on the one hand with intake of diacerein or no intake of SYSADOA or no SYSADOA and on the other hand with intake of NSAID or not. The analysis searched the association between TUA with diacerein and TUA with NSAIDs using a logistic regression model. Three hundred and ninety patients provided 1250 TUA exposed to diacerein. The number of TUA without any SYSADOA was 9277. A total of 2668 TUA of NSAIDs was identified.

The percentage of patients using NSAIDs in patients without any SYSADOA was 23.9 % (2221 from 9277 TUA). The percentage of patients using NSAIDs in patients receiving diacerein was 26.6 % (333 from 1250 TUA). The results of this prospective cohort study did not support the existence of any impact of diacerein use on the utilisation of NSAIDs with an adjusted odds ratio of NSAID use of 1.08 [95% CI: 0.87, 1.33] during the overall exposure period to diacerein.

2.1.3. Meta-analyses

A total of four meta-analyses have been conducted and published on diacerein.

The studies selected for these meta-analyses were not the same because of differences in selection criteria:

- Placebo and/or reference controlled studies,
- Published and/or unpublished studies,
- Usual dose (100 mg/day) or alternative doses,
- Efficacy judged on symptoms and/or structure-modifying effects,
- Availability of ITT results.

The studies included in the different meta-analysis are summarised in the table below.

Studies	Protocol	Duration	Reference	Cochrane 2006	Rintelen 2006	Bartels 2010	Cucherat 2011
Fagnani, 1998	Open, R	6 months	Standard treatment		+		
Chantre, 2000	DB, R	4 months	Harpagophytum	+	+		
Mattara, 1985	DB, R	3 months	NSAID		+		
Pietrogrande, 1985	DB, R	1 months	NSAID		+		
Fiovaranti, 1985	DB, R	2 months	NSAID		+		
Mordini, 1986	DB, R	2 months	NSAID		+		
Mantia, 1987	DB, R	3 months	NSAID		+		
Portioli, 1987	DB, R	3 months	NSAID		+		
Marcolongo, 1988	DB, R	2 months	NSAID		+		
Louthrenoo, 2004	DB, R	4 months	NSAID		+		
Tang, 2004	DB, R	3 months	NSAID	+	+		
Pham, 2004	DB, R	12 months	Placebo + intra-articular injection	+	+	+	
Amor/Dougados, 1994	DB, R	2 months	Placebo/NSAID	+	+	+	+
Ascherl, 1994	DB, R	6 months	Placebo		+		+
Schulitz, 1994	DB, R	3 months	Placebo		+		+
Lequesne, 1994	DB, R	6 months	Placebo	+	+	+	+
Pelletier, 2000	DB, R	4 months	Placebo	+	+	+	+
Dougados, 2001	DB, R	36 months	Placebo	+	+	+	
Pavelka, 2007	DB, R	3 months	Placebo		+	+	+
Goupille&Valat, 2011	DB, R	3 months	Placebo				+

R: randomised; DB: double-blind

COCHRANE review (Fidelix, 2006)

This meta-analysis was conducted under the label of the Cochrane Systematic Review. All randomised or quasi-randomised, placebo- or reference-controlled studies published during the period 1966-2004 were selected, if there was an estimate of variance to be used in meta-analysis. From 25 identified studies, seven were kept for the analysis (see table above). Pain was evaluated in 1228 participants on a visual analogue scale (0-100 mm) and results showed a statistically significant difference in favour of diacerein WMD -5.16 (95% CI: -9.75, -0.57) with an absolute change of five points on the scale, when compared to placebo. When analysed separately by hip OA and knee OA, no difference was detected. According to the Lequesne Impairment Index for function, 1006 participants evaluated did not show improvement ($P > 0.10$). For hip OA, three studies showed a WMD -0.21 (95% CI: -0.82, 0.040). For knee OA, two studies showed WMD -0.95 (95% CI: -2.64, 0.74). The summary WMD was -0.29 (95% CI: -0.87, 0.28).

Two long-term studies, one evaluating hip OA and another evaluating knee OA, analysed structural progression with radiographic measurements of joint space. In hip OA, there was statistical significant slowing of progression in contrast with knee OA that did not demonstrate this reduction. However, the overall effect was very different between studies ($p=0.04$ for hip OA and $p= 0.85$ for knee OA).

The authors concluded that there was 'gold' level evidence that diacerein had a small, consistent benefit in improvement in pain, and that further research was necessary to confirm the short and long-term effectiveness and toxicity of diacerein therapy in OA.

RINTELEN, 2006

This systematic meta-analysis on randomised controlled trials with diacerein was performed to provide an evidence-based assessment of its symptomatic efficacy in the treatment of osteoarthritis.

A total of 23 studies were identified, 19 of which were included. Diacerein was significantly superior to placebo during the active treatment phase (Glass score, 1.50 [95% CI: 0.80, 2.20]). Both diacerein and non-steroidal anti-inflammatory drugs (NSAIDs) were similarly efficacious during the treatment period; however, diacerein, but not NSAIDs, showed a carryover effect, persisting up to 3 months after treatment, with a significant analgesic-sparing effect during the follow-up period (Glass score, 2.06 [95% CI: 0.66, 3.46]). Tolerability assessment revealed no differences between diacerein and NSAIDs, although the latter showed more severe events.

BARTELS, 2010

The objective of this meta-analysis was to estimate the efficacy and safety of diacerein as a pain-reducing agent in the treatment of osteoarthritis (OA), using meta-analysis of published randomised placebo-controlled trials (RCTs).

Six trials (seven sub-studies; 1533 patients) contributed to the meta-analysis, revealing a large degree of inconsistency among the trials ($I^2= 56\%$) in regard to pain reduction: the combined effect size (ES) was -0.24 ([95% CI: -0.39, -0.08], $p=0.003$), favouring diacerein. The statistically significant improvement in function ($p=0.01$) was based on a small amount of heterogeneity ($I^2=11\%$), but presented a questionable clinical effect size (ES=-0.14).

The authors acknowledged that a risk of publication bias could not be excluded. They also concluded that trials with duration of more than six months did not favour diacerein. There was an increased risk of diarrhoea with diacerein (relative risk (RR) = 3.51, $p<0.0001$), and withdrawal from therapy following adverse events (RR=1.58, $p=0.03$).

CUCHERAT, 2011

All randomised, double-blind, placebo-controlled, published or not published studies evaluating diacerein 100 mg/day efficacy in the treatment of symptoms of OA up to May 2011 were selected.

Compared to the previous meta-analyses, Pham (2004) was not included because the primary efficacy criteria was the prevention of the structural progression of OA; moreover both groups received an intra-articular injection of hyaluronic acid; Dougados (2001) or ECHODIAH study was also not included because it had prevention of the structural progression of OA as primary efficacy criteria, and the Brahmachari study published in 2009 was not included because it was a single-blind study.

A total of seven studies (1543 patients) were thus kept for this meta-analysis. All studies had of good methodological quality with a Jadad' score of five. The efficacy data were only extracted during the randomised study period when there was a follow-up.

A total of six of the seven studies eligible for the overall estimation provided data on pain VAS. Diacerein was found superior to placebo in terms of pain with a statistically significant reduction in 100 mm pain VAS of -6.24 mm ([95%CI, -9.03 to -3.45], $p=0.0000$). No heterogeneity was detected ($p = 0.64$, $I^2 = 0.00\%$).

A total of four of the seven studies eligible for this comparison provided data on pain VAS measured as change between baseline and end of the study. The analysis detected a statistically significant difference in favour of diacerein with a WMD of -5.71 ([95% CI: -8.84, -2.57], $p=0.0000$). No heterogeneity was detected ($p = 0.46$, $I^2 = 0.00\%$).

A total of six of the seven studies eligible for this comparison provided data on pain VAS value at the end of the trial/treatment period. The analysis detected a statistically significant difference in favour of diacerein with a WMD of -6.13 ([95% CI: -8.94, -3.33], $p=0.0000$). No heterogeneity was detected ($p = 0.29$, $I^2 = 0.16\%$).

With regards to the secondary outcomes, Lequesne Index was reduced by -1.23 ([95%CI: -2.07; -0.38], $p=0.0043$) compared to placebo with no heterogeneity detected, and the difference in functional impairment judged using the WOMAC function subscale or Lequesne index was in favour of diacerein, with no heterogeneity detected.

Overall discussion on efficacy

As part of this referral procedure, the PRAC reviewed all available data on the efficacy of diacerein medicinal products.

The effects of diacerein on pain and physical functioning of the joints have been evaluated in a number of studies as primary endpoints. The structure-modifying effects of diacerein have also been assessed in few studies as well as its NSAIDs sparing effect (secondary endpoint).

Double blind placebo controlled clinical trials performed during the last 20 years showed heterogeneous results, which may be explained by the usual high placebo effect in this kind of indications. Overall, studies showed a modest but statistically significant effect on pain and physical functioning. However, although double blind was an intended methodological feature of the clinical trials performed with diacerein, it was considered doubtful that blinding was achieved in practice, considering the very apparent effects (urine coloration, diarrhoea) produced by diacerein. This point was not addressed in any of the trials. In addition, the missing data and their handling were considered problematic from a statistical point of view.

The evidence obtained from different meta-analysis of the clinical trials performed with diacerein showed a small, consistent, beneficial effect of diacerein in the treatment of OA of the knee and hip with different criteria for the inclusion of the clinical trials in the meta-analyses. However, the quality of the studies was heterogeneous and publication bias could not be excluded since only published trials and non-published trials sponsored by the companies were included in the systematic reviews.

Regarding the latest meta-analysis performed (Cucherat, 2011), it was noted that two important studies, both in terms of sample size and of treatment duration, had not been included in the meta-analysis: (i) ECHODIAH study (Dougados *et al.* 2001) with 255 patients in the diacerein arm and 252 under placebo for 3 years of treatment, and (ii) Pham study (2004) which included 85 patients in the diacerein arm and 85 under placebo during one year. The primary objective of these two studies was on structural impact but they also assessed the effect of diacerein on pain as secondary endpoint. It is noteworthy that these two studies did not evidence efficacy of diacerein on pain or physical functioning. In both cases, the study authors reported no difference between groups on analgesic consumption.

The data available in order to ascertain the efficacy of diacerein include some double-blind clinical trials versus placebo with the accepted primary efficacy criteria of efficacy for symptomatic treatment of osteoarthritis. Although some of these studies show a modest but statistically significant delayed symptomatic effect they were of limited value from the clinical point of view and also presented methodological issues.

The main studies that evaluated the effect of diacerein on structural progression or disease modifying properties in OA were the Dougados study and the Pham study (*Pham et al.*, 2004). Only the Dougados study showed efficacy on variables related to a beneficial impact of diacerein on structural progression or disease modifying properties in OA. In the second clinical trial, diacerein was included in one of the control groups in a trial intending to demonstrate the effect of hyaluronic acid intra-articular injections in OA progression which was not demonstrated. The currently available data were therefore not sufficient to conclude on the structure-modifying effects of diacerein in osteoarthritis and no data were available regarding a potential effect of diacerein for delaying surgery.

With regards to the NSAIDs sparing effect of diacerein, it was analysed as secondary end-point in a number of double-blind randomised clinical trials with diacerein 100mg/day in osteoarthritis of the knee/hip provided by the MAHs. A reduction in the use of NSAID was only shown in one study and therefore a sparing effect of diacerein on NSAIDs could not be confirmed. However, a sparing effect on paracetamol use was demonstrated in 4 out of 8 clinical trials.

2.2. Clinical safety

Diacerein's safety profile has been the subject of previous national reviews which looked at digestive side effects, mainly melanosis coli; severe cutaneous adverse reaction (SCAR) labelled toxic epidermal necrolysis (TEN); and the possibility of occurrence of liver abnormalities with exceptional cases of hepatitis with diacerein.

In 2012, the ANSM initiated a review of the benefit-risk of diacerein containing medicinal products which underlined the occurrence of very frequent digestive disorders, cases of hepatitis and serious skin reactions in patients treated with diacerein.

The PRAC reviewed all available data from clinical studies, published literature, and post-marketing experience on the safety of the diacerein containing products, in particular in relation to the risk of hepatotoxicity, gastro-intestinal disorders and cutaneous disorders.

A summary of the relevant data is provided in this report.

2.2.1. Hepatotoxicity

2.2.1.1. Clinical studies

Available results of all clinical studies with oral diacerein sponsored by the MAH of the originator as well as published studies by other sponsors were reviewed. Studies where diacerein was used as a comparator were also included.

Seven studies showed abnormalities of liver tests. These were mostly characterised by mild/moderate liver enzyme increase (alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) < 5 ULN) without bilirubin increases.

Overall, 29 hepatic reactions were reported in clinical trials, half of them (15) having been reported in the longest duration study, the ECHODIAH study (follow-up duration of 3 years).

In this study, ALAT, ASAT and Gamma-glutamyl transpeptidase (GGT) increases were reported as AEs in 11 patients receiving diacerein (4.3%) versus seven patients receiving placebo (2.8%).

There were four serious hepatobiliary events in the diacerein group (1.6%): two cases of cholecystitis (0.8%), one case of non-icteric hepatitis (0.4%) and one case of cholelithiasis (0.4%) versus three cases of cholecystitis (1.2%) in placebo group.

The case of "non-icteric hepatitis" was reported in a patient with a history of viral hepatitis and three episodes of jaundice and occurred in a context of serious acute pancreatitis with cholecystitis related to an obstruction due to a biliary calculus.

Two of the four cases of hepato-biliary reactions (0.8%) resulted in diacerein treatment termination.

In the Pelletier study, hepatic events occurred in the group treated with diacerein 50 mg/day only.

In the Ascherl study, seven cases of hepatic events were observed in the diacerein group (11.9%), versus three cases under placebo (5.8%). The most frequent event (four patients, 6.8%) in diacerein group was elevation of GGT activity, not observed in the placebo group. Other hepatic AEs in the diacerein group were high bilirubin (two patients, 3.4%), cholelithiasis (one patient, 1.7%) and biliary pain (one patient, 1.7%). No elevation of hepatic enzyme (ASAT, ALAT, GGT) or bilirubin was observed in the placebo group.

In studies where hepatic reactions were observed, the incidence ranged from 0.30% to 11.86% (pooled together: 1.69%).

2.2.1.2. Spontaneous reports

A total of 979 cases of adverse events have been reported to the MAH of the originator. Of them, 92 cases belong to the Standardised MedDRA Queries (SMQs) hepatic disorders, equivalent to 9.36%. These 92 case reports contained 247 adverse reactions, of which 146 reactions were hepatic, whereas other 101 reactions belonged to other SMQs. Twenty four cases were considered as serious. The percentage of hepatic disorders was higher in the female population (64%) than in the male population (35%). In one case the sex was unknown. The duration of diacerein therapy ranged from 5 days to 730 days and the mean duration was 112 days. Therapy duration was unknown in 42 cases.

Further evaluation of these cases showed that out of the 92 cases, 15 cases corresponded in fact to a coagulation disorder (prothrombin time or International Normalized Ratio (INR) variation in 14 cases and vasculitis in 1 case), which were not recognised as real liver injury in absence of laboratory liver test abnormalities. Therefore, 77 cases within the post-marketing surveillance were considered hepatic reactions. The causality of diacerein for these 77 cases according to Roussel Uclaf Causality Assessment Method (RUCAM) scoring were: 3 cases probable, 31 cases possible, 15 cases unlikely, 4 cases excluded, 24 cases were not assessable.

The most frequent reactions were liver function test abnormalities which were reported in 39 cases. Among the remaining cases there were cases of hepatic steatosis (including one associated with pancreatitis necrotizing in a patient with a history of alcoholism), hepatitis (including one associated with microlithiasis, one with cholelithiasis, one with erythema multiforme and eosinophilia and two with icterus), cholestatic hepatitis, hepatic cytolysis (the biopsy of one of them suggested an autoimmune hepatitis), autoimmune hepatitis, liver injury, and hepatic failure. The daily dose was reported in 26 cases, being 100 mg in 14 cases and 50 mg in 12 cases. Among these cases, there were 23 cases with a positive dechallenge and one with a positive rechallenge.

The case of hepatic failure had a fatal outcome (described below in the publication section; *Renan et al.* 2001) and a close temporal association with diacerein; other alternative causes were ruled out.

Three additional cases of hepatitis were reported by another MAH.

2.2.1.3. Literature data

Two cases of serious hepatic reactions attributed to diacerein were published.

The first case was an acute hepatitis ascribed to diacerein reported in a 65-year-old woman (71 kg, 157 cm) who was hospitalised due to acute epigastric and retrosternal pain with pruritus which occurred seven days after onset of diacerein treatment at 100 mg/day. Liver biopsy performed at 19 days after clinical symptoms onset showed hepatocellular and canalicular cholestasis with inflammatory infiltration, mostly lymphocytic. Enzyme activities returned to normal after diacerein treatment stopped, whereas pruritus persisted for more than a month, despite cholestyramine and corticosteroid treatment. Antinuclear antibodies were no longer detectable. In this case, no other reasons of hepatitis except for suspected adverse reaction to diacerein could be found (*Vial et al. 1997*).

The second publication concerned a fatal case of a 68-year old man who had started diacerein treatment at a dose of 50 mg once a day after an unsuccessful attempt (gastric intolerance) of diclofenac treatment and was hospitalised about 45 days after treatment onset due to jaundice, enzymatic signs of cytolysis and cholestasis, and biochemical signs of hepatic failure (prothrombin ratio of 16%), with fever, without pruritus, without ascites and without consciousness disturbance. Imaging studies showed hypertrophic caput pancreatic and no signs of portal hypertension. Few days later, the signs of hepatic failure aggravated followed by hepatic coma. The patient died one month after onset of symptoms, in course of haemorrhagic shock. In this case, no other reasons for hepatitis except for suspected adverse reaction to diacerein could be found (*Renan et al. 2001*).

2.2.1.4. EudraVigilance database

Nineteen cases of hepatic disorders were identified in EudraVigilance database. Of them, 10 cases were already described by the MAHs. The remaining cases included one case of liver injury in a patient with CREST syndrome, two cases of cholestatic hepatitis, three cases of hepatitis, a case of hepatocellular injury and two cases of hepatic enzymes increased.

2.2.2. Gastrointestinal disorders

2.2.2.1. Clinical studies

Available results of all clinical studies with oral diacerein sponsored by MAHs as well as published studies by other sponsors were considered. Studies where diacerein was used as a comparator were also included.

Diarrhoea-related reactions

The proportion of diarrhoea cases rated 'severe', regardless of their seriousness, was between 4.1% and 42.9% among all diarrhoea cases reported in analysed studies. The difference may be due to subjectivity of severity grading, various levels of safety data collection sensitivity, and different sample sizes.

The incidence of diarrhoea reported in therapeutic clinical trials under diacerein treatment ranged from 0% to 54.4%. In total, 13309 patient data were taken into account. Almost 60% (59.53%) of patient data came from just one study, the Indian post-marketing study by Sharma et al. (2008), which reported a very low frequency of diarrhoea (2.3%). Incidence rate for diarrhoea and dropped out calculated by pooled studies (excluding Sharma study) was 25.06% and 7% respectively.

In most cases diarrhoea was reported as a stand-alone adverse event, or, incidentally, in combination with other gastrointestinal or non-gastrointestinal events. No particular pattern of associated disorders could be detected. Positive dechallenge was reported as a rule.

If in most of the cases reported in clinical trials, diarrhoea was a moderately early onset reaction, occurring after 1-2 weeks of treatment, and was mild to moderate and transient, some studies demonstrated that the number of patients with diarrhoea decreased with the time but the number of persistent diarrhoea and chronic diarrhoea remained significant in patients treated by diacerein, which was of concern.

This was notably shown in the study by *Fagnani et al.* where the peak frequency of diarrhoea (17.4%) was at day 15 after the treatment onset and then decreased, but the level of diarrhoea remained significant (12.6% at day 45, 9% at month 3 and 13.5% at month 6). Moreover 11 patients (out of 107 patients in the diacerein group) had stopped the treatment due to diarrhoea; this may explain in part the decrease in the frequency of diarrhoea over time. About 10% of patients had presented with persistent diarrhoea 6 months after diacerein intake.

In the Amor and Dougados study, about 25% of patients (8/24) experienced persistent diarrhoea at day 45 of treatment, and in the Goupille and Valat study, 25% of the patients experienced diarrhoeas for more than 29 days.

This was also shown in the Lesquesne study in the ITT analysis. The change in number of patients with diarrhoea over time was 32.1% at month 1, 35.1% at month 2, 27.3% at month 4, 21.9% at month 6, 5.3% at month 9. In this study the diarrhoea had a mean cumulative duration for the trial of 87 days.

According to the ECHODIAH study, diarrhoea occurred within the first two weeks (mean delay 8.5 days). This delay was confirmed by the data described in the Goupille and Valat study (median 5.5 days but with 25% of patients with a time to onset superior to 25.5 days) and in the Lequesne study (mean 6 days).

In the study 95305N, a comparative study of the efficacy and tolerability of two therapeutic regimens of diacerein (usual treatment (50 mg twice a day) for 3 months or progressive treatment (50 mg once a day for one month; then 50 mg twice a day for two months) as compared to placebo for the treatment of osteoarthritis of the hip and/or the knee. The time to onset of diarrhoea in the diacerein group treated with 50 mg twice a day was 15.8 days (26.5% of patients) but in the group treated only with 50 mg once a day, this delay was increased to 31.4 days (17.3% of patients).

Incidence data on diarrhoea and related dropouts from some of the most relevant studies are presented in the table below:

Reference (year)	Control	Nr. randomised diacerein/control	Incidence of diarrhea (%)		Dropout rate due to diarrhea (%)	
			Diacerein	control	Diacerein	control
Amor&Dougados (Nguyen, 1994)	tenoxicam	142/146	37	5.5	3.5	0
Marlongo	naproxen	308/103	8	0	1.9	0
Ascherl (1994)	Placebo	59/52	22	1.9	1.7	0
Schulitz (1994)	Placebo	40/40	15	10	5	0
Lequesne (1998)	Placebo	90/93	37.8	11.8	6.7	1.1
Pelletier (2000)	Placebo	111/125	17.5	13.6	2.7	2.4
Dougados (2001) (ECHODIAH)	Placebo	255/252	45.9	12.3	11.8	1.6
Pavelka (2007)	Placebo	84/84	15.5	8.3	unknown	unknown
Jarayam(2005)	diclofenac	117/116	8.5	12	0	0
Goupille&Valat (2011)	Placebo	249/224	17.7	8	5.2	2.2
Louthrenoo (2007)	Piroxicam	86/85	36	10	0	0
Zheng (2006)	diclofenac	112/111	17	9.9	3.6	0

The incidence of diarrhoea has also been subject of calculations in few meta-analyses:

- The meta-analysis of *Rintelen et al.* (2006) showed that about 39% of patients (1328 pooled) in diacerein groups experienced at least one episode of diarrhoea or soft stools, versus about 12% (of 1309 patients pooled) in placebo groups.
- In the meta-analysis of *Fidelix et al.* (2006) where 1083 patients using diacerein were pooled, comparisons demonstrated that diarrhoea was present in 459 patients, a rate of about 42%. Its severity was mild-to-moderate and occurred in the first two weeks of the treatment.
- In its meta-analysis, Bartels estimate that one in four patients would have diarrhoea if diacerein was used instead of placebo (RR=3.51) (*Bartels et al.*, 2010).

It was shown in the Pelletier study, that the laxative properties of diacerein were dose-dependent.

Other serious gastrointestinal reactions

There are few other cases of gastrointestinal serious adverse events not involving diarrhoea in patients treated with diacerein or for which causal relationship was not excluded, documented in clinical studies.

Most of the cases were reported in the ECHODIAH study, where serious gastrointestinal adverse events were more frequent in the diacerein arm (14 cases/255) than in the placebo arm (3 cases/252, $p=0.007$).

The 14 serious gastrointestinal cases reported included diverticulosis, abdominal pain, infectious enteropathy, gastroenteritis, haemorrhoids, hiatus hernia, megadolichocolon, intestinal occlusion, intestinal polyp, ulcerative colitis, duodenal ulcer and perforated gastric ulcer.

2.2.2.2. Spontaneous reports

Among the 979 adverse events reported with diacerein by the MAH of the originator product, 87 cases (8.89%) concerned serious gastrointestinal adverse reactions: 22 cases were related to diarrhoea (25.29%) and 65 cases (74.7%) were related to others serious gastrointestinal reactions.

Diarrhoea

A total of 22 serious cases of diarrhoea were reported. Eleven cases (50%) were reported in patients of 18 to 65 years of age and ten cases (45%) occurred in patients over 65 years. In one case, age was not provided. The mean age was 67 years. Most of the cases were reported in women (88%).

Therapy duration varied from six to 570 days. In half of the cases diarrhoea appeared in the first 15 days of treatment. Daily dose of diacerein was 100 mg in 12 cases and 50 in eight cases. In two cases dose was unknown.

In most of the cases (19/22) diarrhoea was associated with other adverse reactions, such as abdominal pain, colitis, melanosis coli, gastrointestinal bleedings and pancreatitis. The outcome was reported as recovered in most of the cases.

In two cases that concerned elderly, the patient experienced dehydration. One case was fatal, and occurred in a 79-year-old female with a medical history of arterial hypertension and cardiac arrhythmia. The other case involved a 90-year-old female who experienced diarrhoea, abdominal pain, marked dehydration with arterial pressure of 80/40 mmHg and severe hypokalaemia. The events appeared four days after starting therapy with diacerein. Dehydration and severe hypokalaemia were

successfully managed by rehydration and potassium supply. Diacerein was discontinued. Other alternative aetiologies were ruled out (*Blondon et al.1995*).

Two additional case of severe diarrhoea were described by another MAH, including one case associated with dehydration in a 68 year-old male treated with diacerein for an unknown indication. Five days after the initiation of treatment the patient experienced an acute episode of diarrhoea, syncope and dehydration. A positive dechallenge for diacerein was reported. The second case of diarrhoea was reported in a 52-year-old male who experienced diarrhoea after the first ingestion of diacerein 50 mg/day. After 3 days diacerein was withdrawn but the event persisted during weeks, being refractory to treatment. Clinical tests were normal (biopsy, colonoscopy, echography, bacterial cultures, parasites, biochemistry).

Other serious gastrointestinal reactions

Among the 979 cases collected by the MAH of the originator product, a total of 65 serious cases not including diarrhoea were reported, encompassing 148 adverse reactions. The most common adverse reactions were pancreatitis (14 cases), and gastrointestinal haemorrhage (21 cases).

Age ranged between 18 and 65 years in thirty-three cases (50.7%) and over 65 years in 31 cases. In one case age was unknown. Most cases occurred in women: 40 (61%) vs. 25(38%).

Therapy duration on diacerein varied between two and 1080 days. Diacerein was used at the dose of 100 mg/day in 25 cases, and 50 mg/day in 23 cases. In one case the patient received 200 mg/day, and in another, 60 mg/day. In twelve cases the dose received was unknown.

In 40 cases the outcome was reported as 'recovered': and two patients recovered with sequelae, in 4 cases, the outcome was reported as 'recovering' .Eight did not recover. In 11 cases the outcome was not provided.

Among the patients who experienced upper gastrointestinal bleedings, one had a history of gastrointestinal ulcer, six patients were concomitantly treated with NSAIDs, and one patient was taking prednisone; in most of the cases, no further information was provided.

Three patients who developed diarrhoea experienced also a gastrointestinal bleeding. In two cases the patients developed diarrhoea and gastrointestinal bleeding/rectal bleeding 15 days or one month after starting therapy with diacerein. In both cases neither relevant medical history for gastrointestinal bleeding nor concomitant drugs were reported. In both cases there was a positive dechallenge.

Cases of pancreatitis involved nine females and five males aged from 37 years to 94 years of age. Time to onset ranged from one day to one year, but in 60% of the cases it was during the first month of treatment.

Additional cases reported by another MAH included a case in a 76-year-old female patient who experienced gastrointestinal haemorrhage while receiving diacerein at 50 mg/day, and a case in a 52-year old female patient who reported a haematochezia a week after initiating treatment with diacerein at 100 mg/day. Both cases had positive dechallenge.

Another case of pancreatitis in a 46-year-old-woman treated with diacerein was also reported. The patient had neither history of lithiasis nor of alcohol consumption.

2.2.2.3. EudraVigilance database

There were 24 cases of serious gastrointestinal adverse reactions collected in the EudraVigilance database. Of these, eight cases reported diarrhoea. One case described dehydration associated with diarrhoea and vomiting and occurred in an 86-year-old female. Scarce information was available to

assess causality and this case was not described by the MAHs. From the remaining cases, it was not possible to identify if they were duplicates of those presented by MAHs, although some characteristics were shared (appeared at the initiation of treatment, occurred associated with other reactions and had a positive dechallenge).

Other serious gastrointestinal reaction collected included four cases of gastrointestinal bleeding, one of retroperitoneal haemorrhage described by one MAH and two cases of pancreatitis described by another MAH.

2.2.3. Cutaneous reactions

Cutaneous reactions have been reviewed by several MAHs. Additional information was provided by EudraVigilance database and RegiSCAR.

In clinical trials the incidence of cutaneous reactions varied from 0.32% to 12%. Rash, pruritus, eczema were the most common cutaneous reactions reported in clinical trials.

The available post-marketing data revealed four cases of erythema multiforme two cases of Stevens-Johnson syndrome (SJS) and three cases of toxic epidermal necrolysis (TEN).

Scarce information was available for cases of erythema multiforme and different diagnoses were suggested in two cases (DRESS, maculopapular eruption). Nevertheless, a compatible time onset and positive dechallenge suggest a causal relationship of diacerein with these reactions.

Among the cases of SJS, one had a compatible time onset, but scarce information was available. The other case, from RegiSCAR, concerned a patient who was also receiving sulfamethoxazole a drug which is known to be associated with SJS/TEN and the causality of diacerein was considered very unlikely by RegiSCAR.

With regard to TEN cases, one was fatal (*O Dereure et al, Dermatology 1998; 196: 431*), although no other drugs were identified as possible alternative cause, time onset for diacerein was longer (three months) than the usually accepted for SJS/TEN. In the two remaining cases a compatible time onset was described. One case reported as TEN was confirmed by biopsy and the other had scarce information but the according to the expert there was not mucous involvement.

In summary, some cases of severe cases of cutaneous reactions (SJS, TEN) have been reported but the available information (time onset no compatible, other medications, diagnosis not confirmed) did not permit to conclude on an association between diacerein and SJS/TEN.

Overall discussion on safety

The PRAC reviewed all available data from clinical studies, published literature, and post-marketing experience on the safety of the diacerein containing products in relation to the risk of hepatotoxicity, gastro-intestinal disorders and cutaneous disorders.

Diacerein as other anthraquinone derivatives has a hepatotoxic effect which mechanism is unknown. The data from clinical studies showed no significant differences in hepatic disorders between diacerein and the placebo group but it was noted that, when present, hepatic disorders were in most of cases in the diacerein group.

However, evidence for hepatic reactions beyond reversible transaminase elevations was reported in the post-marketing setting, with spontaneous reports of symptomatic acute liver injury. About 10% of adverse drug reactions (ADR) reported were hepatic disorders and in over 68% of these cases, diacerein was the only drug suspected. Moreover, two cases raised concerns: one fatal hepatitis case in

which no other reasons of hepatitis except for diacerein could be found; and one case of acute hepatitis with suggestive chronology and no other explanation.

With regards to the risk of gastrointestinal disorders, diarrhoea was a common and expected reaction of diacerein. A laxative effect was observed in up to 50% of the diacerein-treated patients in clinical studies. Some studies revealed that 25% patients with diarrhoea during diacerein treatment experienced chronic diarrhoeas, defined by diarrhoea persisting more than 4 weeks. The high dropout rate due to diarrhoea in clinical trials showed that the acceptability of the treatment was worse in the diacerein group than in the placebo group.

In spontaneous reports, one quarter of serious gastrointestinal cases were related with diarrhoea. The PRAC also noted that spontaneous notifications reported serious cases of diarrhoea with dehydration and electrolyte disorders. Some cases of hospitalisation to further investigate the event of diarrhoea were also reported. This constituted a concern for the PRAC and it has to be noted that these investigations exposed the patients to invasive examination (i.e. colonoscopy with biopsy). In addition, the management of diarrhoea could also expose patients to symptomatic treatments.

Finally, with regards to the risk of cutaneous disorders, safety concerns were raised with diacerein following a publication of a fatal case of a toxic epidermal necrolysis, with diacerein being the most suspected drug for the events. The present review showed that rash, pruritus and eczema were the most common cutaneous reactions reported in clinical trials but available post-marketing data revealed cases of erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Because of the limited information available on these cases, the PRAC could not conclude on this risk but a cutaneous toxicity of diacerein could not be excluded.

2.3. Risk management plan

In view of the safety concerns raised with diacerein, the MAHs proposed a number of risk minimisation activities.

They notably proposed to restrict the patient population, amending the indication to “symptomatic treatment for hip and knee osteoarthritis with delayed effect”, and adding the recommendation not to treat patients with rapidly progressive hip osteoarthritis, as they may have a weaker response to diacerein.

In addition, the MAHs proposed to reduce the posology recommendation at the start of the treatment to half a dose (50 mg once a day) for the first 2 to 4 weeks, the time window in which most of transient diarrhoea are reported, and to make amendments to the section 4.4 warning and precautions of the SmPC to reflect in particular that no laxatives should be used in concomitance to diacerein and highlight the risk of hepatotoxicity associated with diacerein. Amendments of section 4.8 of the SmPC were also proposed.

Finally, it was proposed to develop a risk management plan for diacerein and enhance communication about the risks associated with diacerein.

The PRAC, having considered the data submitted by the MAHs, considered that the proposed risk minimisation activities were not appropriate to reduce the risks to an acceptable level, taking into account the suggested idiosyncratic mechanism of diacerein hepatotoxicity and the lack of data on the impact of a dose reduction with regards to the diminution of incidence and severity of diarrhoea.

3. Overall discussion and benefit-risk assessment

The PRAC reviewed all the available data on the efficacy and safety of diacerein-containing medicines in particular data in relation to the risk of hepatotoxicity, gastrointestinal disorders and cutaneous reactions provided by the MAHs in writing and in the oral explanations as well as data retrieved in the EudraVigilance database.

The data available in order to ascertain the efficacy of diacerein include some double-blind clinical trials versus placebo with the accepted primary efficacy criteria for symptomatic treatment of osteoarthritis. Although some of these studies showed a modest but statistically significant delayed symptomatic effect they were of limited value from the clinical point of view and also presented methodological issues.

The results of the study on impact on radiologic signs were not considered sufficient to conclude on a modifying effect of diacerein and future studies would be needed to improve the understanding of the clinical relevance of these results. No data were available regarding a potential effect of diacerein for delaying surgery. Also, the data presented regarding a potential sparing effect of NSAIDs with diacerein failed to demonstrate such an effect.

Regarding safety, the review found that the most frequently reported reactions with diacerein were, as expected, gastrointestinal disorders, especially diarrhoeas, which were frequently severe and leading to complications such as dehydration and disturbances of fluid and electrolyte balance. Furthermore, cases of hepatic enzymes elevations have been reported and as well as serious cases, including a fatal hepatic reaction in a patient treated with diacerein.

Having considered the overall submitted data provided by the MAHs in writing and at the oral explanation, the PRAC concluded that the benefit-risk balance of diacerein containing products is not favourable in the currently approved indications.

Based on those conclusions, the PRAC recommended the suspension of the marketing authorisation for diacerein containing medicinal products.

4. Re-examination procedure

Following the adoption of the PRAC recommendation during the November 2013 PRAC meeting, a re-examination request was received from two of the MAHs involved in the procedure, TRB Chemedica and Laboratoires Negma on 19 and 23 November 2013, respectively.

The MAHs considered that there is adequate data supporting the efficacy of diacerein in the symptomatic treatment of osteoarthritis of the hip and the knee and proposed further risk minimisation measures to reduce the risk of diarrhoea and potential risk of hepatic reactions associated with diacerein.

One of the MAHs also expressed concerns over legal aspects of the referral procedure. However the PRAC is a scientific committee and that while it operates within the legal framework, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the PRAC, and therefore the re-examination of the referral procedure under Article 31 of Directive 2001/83/EC only focused on the scientific grounds for re-examination addressed by the MAH.

Detailed grounds for re-examination submitted by the MAHs

- **Efficacy aspects**

In their grounds, the MAHs outlined the results of the double blind randomised clinical trials and re-described the methodology and results of four meta-analyses. Both MAHs reiterated that diacerein is efficacious in the symptomatic treatment of osteoarthritis, with modest but consistent amplitude of the treatment effect, based on evidence from randomised controlled trials and four meta-analyses of randomised controlled trials showing a significant beneficial clinical effect on pain and physical functioning.

- **Safety aspects**

The MAHs reviewed the laxative properties of diacerein with particular focus on the severity of diarrhoea and concluded that diacerein-induced diarrhoea was usually mild or moderate, occurring most commonly during the first 2 weeks of treatment and resolving after treatment discontinuation. Similarly, the MAHs discussed the risk of hepatotoxicity, re-analyzing all serious and non-serious cases involving any signs suggestive of hepatic abnormality and concluded that the hepatotoxicity of diacerein remained a potential risk.

In their grounds for re-examination, both MAHs proposed new measures to minimise the occurrence of diarrhoea and hepatic reactions.

PRAC conclusions on grounds for re-examination

The PRAC had considered the totality of the data submitted by the MAHs in the context of the initial referral procedure. Notwithstanding this, and given the new proposals from the MAHs on additional measures to minimise the risks, the PRAC carried out a new assessment of the available data in the context of the re-examination.

- **Efficacy**

The efficacy of diacerein in the symptomatic treatment of osteoarthritis of hip and knee was supported by five double-blind, randomized clinical trials (Amor-Dougados study, Lequesne study, Pelletier study, Pavelka study and Singh study). In these studies diacerein has shown superiority versus placebo for the end-point pain relief. As primary endpoints the Visual Analogue Scale (VAS) (0-100mm) or the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC A) for assessment of pain on movement were used, which are validated methods and can be accepted. Furthermore in three of these studies (Lequesne study, Pavelka study and Singh study) diacerein had showed a statistical significant effect versus placebo in VAS from one to three months after cessation of the treatment and could support the theory of a carry-over effect. In two clinical trials (Ascherl study, Schulitz study) function disability measures have been used as primary end-points with statistical significant results in favour of diacerein compared to placebo. It was shown that the first beneficial effects on osteoarthritis symptoms can be seen after 2 – 4 weeks of continuous use and that symptomatic effect occurs after 4 to 6 weeks (Amor-Dougados study, Lequesne study, Pelletier study, Pavelka study and Singh study). Considering this delayed initial onset of action, the PRAC was of the view that diacerein should not be recommended in patients with rapidly progressive hip osteoarthritis, as they may have a weaker response to diacerein.

It was reiterated that structure-modifying effects of cartilage by diacerein in OA and long-term efficacy had not been demonstrated by the presented studies. Furthermore and as previously concluded, a

paracetamol sparing effect (in four out of eight trials) and a sparing effect on NSAIDs (in one trial) could be detected, but further data would be needed as proof of evidence.

All clinical trials mentioned were performed as double-blinded, most of them placebo controlled with appropriate endpoints, and showed a modest but statistically significant effect of diacerein in support of the approved indication OA of the knee and hip. Although these studies were not flawless, the handling of missing data and the blinding of the studies were discussed as part of this re-examination and it was concluded that the last observation carried forward (LOCF) method was acceptable and that all feasible measures had been taken to ensure the blinding of the studies.

In summary, it was concluded from the data obtained from clinical trials and the results of the meta-analyses that diacerein shows a modest but statistically significant effect in the treatment of osteoarthritis of the knee and hip, with delayed effect.

- **Safety**

The PRAC reviewed the available safety data and confirmed its previous conclusions that the use of diacerein-containing products is associated with safety concerns such as frequent cases of severe diarrhoea and cases of potentially serious hepatotoxicity; a risk of cutaneous reactions could not be excluded.

With regard to the risk of diarrhoea, it was noted that in all presented clinical trials the most frequently reported events with diacerein, when used as recommended (100mg/day), were loose stools and diarrhoea. The incidence of diarrhoea reported in therapeutic clinical trials (13309 patients) under diacerein treatment ranged from 0% to 54.4%. In addition, some studies revealed that 25% patients with diarrhoea during diacerein treatment experienced chronic diarrhoeas, defined by diarrhoea persisting more than 4 weeks. Although the incidence of adverse events was higher in the groups treated with diacerein than in the placebo groups, in the majority of cases diacerein-induced diarrhoea started in the first 2 to 4 weeks after treatment initiation, as shown in the ECHODIAH study (Dougados 2001), the longest study conducted with diacerein (3-year), in which occurrence of diarrhoea under diacerein treatment was observed generally at the start of treatment (median: 8.5 days) and in which the population receiving diacerein behaved similarly to the placebo arm several weeks after treatment onset. The high dropout rate (6.9%) due to diarrhoea in clinical trials showed that the acceptability of the treatment was worse in the diacerein group than in the placebo group. However, this may be explained by the late onset of action of diacerein and the early start of diarrhoea. In all cases the diacerein-induced diarrhoea was reversible after cessation of treatment.

In order to minimize this risk, the proposal to reduce the posology recommendation at the start of the treatment to half a dose (50 mg once a day) for the first 2 to 4 weeks was reconsidered. Efficacy of the 50mg dose was demonstrated in the Pelletier dose-finding study (2000) which showed that the laxative properties of diacerein were dose-dependent and confirmed that patients treated with dosages of 50 mg/day diacerein showed favourable results for the primary criterion, VAS assessment of pain on movement. However, the PRAC was still concerned by the lack of data on the impact of a dose reduction on the diminution of incidence and severity of diarrhoea and was therefore of the view that this measure alone would not be sufficient to minimise the risks of diarrhoea complications.

The PRAC therefore considered that patient populations more vulnerable to diarrhoea complications, such as patients aged 65 years and above should not be recommended treatment with diacerein. The PRAC also concluded that warnings about concomitant treatment with medicines that can lead to hypokalaemia, such as diuretics or cardiac glycosides should be reflected in the product information. A warning against concomitant use of laxatives was also introduced as well as a recommendation to stop treatment as soon as diarrhoea occurred.

With regards to the risk of hepatotoxicity, and as previously assessed, several hepatic events, including serious hepatic reactions and one fatal case of hepatitis have been reported with diacerein. The mechanism of diacerein hepatotoxicity is unknown but an idiosyncratic mechanism is suggested. Evidence for hepatic reactions beyond reversible transaminase elevations was reported in the post-marketing setting, with spontaneous reports of symptomatic acute liver injury. Pooled data from clinical studies on diacerein indicate frequency of any hepatic reaction as 0.50% (31 out of 6259 patients analysed). Among those 31 reactions, two were accountable for drug-induced liver injury (DILI) (one case of hepatitis and one transaminase elevation of > 5x). As many as 21 cases were mild enzyme elevations, not accountable for DILI. In addition, 7 biliary events and one hepatic nodules event were seen. Thus, DILI incidence was calculated at 0.03%. Post-marketing data showed that most of the cases of liver disorders reported in association with the use of diacerein involved reversible increase of transaminases. However, and as described above, two cases of acute hepatitis in association with diacerein use were reported in the literature, one of which had a fatal outcome.

To prevent the risk of hepatotoxicity, the PRAC was of the view that diacerein should be contraindicated in patients with current and/or history of liver disease and therefore, and that patient should be screened for major causes of active hepatic disease before starting the treatment. The PRAC also considered that the product information should reflect the recommendation to monitor signs of hepatic injury and caution should be exercised when diacerein is used concomitantly with other medicinal products associated with hepatic injury. Patients should be advised to limit their alcohol intake while on treatment with diacerein. In addition treatment with diacerein should be stopped if elevation of hepatic enzymes or suspected signs or symptoms of liver damage are detected. These warnings and recommendations were introduced in the relevant sections of the SmPC. In addition, the frequency of cases of elevated hepatic enzymes in serum is now reflected in the section 'Undesirable effects' of the Product Information.

Finally, with regards to the cutaneous reactions and as previously concluded, rash, pruritus and eczema were the most commonly reported in clinical trials. The PRAC considered that these reactions should be appropriately reflected in the product information and therefore recommended the addition of the frequency of these events (> 1/100 and < 1/10) in section 'Undesirable effects' of the Product Information.

In view of the above described safety profile and the subsequent PRAC recommendations, and in order to ensure adequate selection of the patients in terms of diagnosis, indication, alternative treatments and communication of benefit/risk at start of treatment, the PRAC also recommended that diacerein should only be initiated by specialists experienced in the treatment of osteoarthritis.

To ensure adequate monitoring of the adverse reactions of diacerein-containing medicinal products and consequently evaluated the effectiveness of the implemented risk minimisation measures, the PRAC recommended that periodic updated safety reports (PSURs) for diacerein-containing medicinal products, including generics, should be submitted on a yearly basis. The list of EU reference dates (EURD list) will be amended accordingly.

Overall conclusion of the re-examination procedure

Based on the totality of the data available on the safety and the efficacy of diacerein, and considering all the new risk minimisation measures proposed during the re-examination procedure, the PRAC concluded that the benefit-risk balance of diacerein-containing medicinal products remained favourable in the symptomatic treatment osteoarthritis, subject to the agreed changes to the product information and conditions.

5. Changes to the product information

The PRAC recommended that amendments to sections 4.1, 4.2, 4.3, 4.4, 4.5 and 4.8 of the Summary of Product Characteristics (SmPC) of all diacerein-containing medicinal products should be introduced. Corresponding changes to the package leaflet should also be introduced (see attachment 9).

6. Conclusion and grounds for the recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for diacerein containing medicinal products;
- The PRAC reviewed all the available data on the efficacy and safety of diacerein-containing medicines in particular data in relation to the risk of hepatotoxicity, gastrointestinal disorders and cutaneous reactions provided by the MAHs in writing and in the oral explanations;
- The PRAC considered the grounds for re-examination provided by the MAHs in writing and in the oral explanations;
- The PRAC considered that the available data supporting the use of diacerein have shown a modest but statistically significant effect in the treatment of osteoarthritis of the knee and hip, with a delayed effect. However, treatment with diacerein is not recommended in patients with rapidly progressive hip osteoarthritis, as they may have a weaker response to diacerein.
- The PRAC considered that available data from pre-clinical studies, clinical trials, post-marketing spontaneous case reports, and published literature have shown that the use of diacerein-containing products is associated with safety concerns such as frequent cases of severe diarrhoea and cases of potentially serious hepatotoxicity; a risk of cutaneous reactions could not be excluded.
- The PRAC considered that several new measures should be implemented to minimise these risks. These included a recommendation to start treatment at half the normal daily dose, a contraindication in patients with a history and/or current liver disease and a clear recommendation for patients to stop treatment as soon as diarrhoea occurs. Also, diacerein is no longer recommended for patients aged 65 years. In addition, given the gastrointestinal risk and potential risk of hepatic reactions, the PRAC considered necessary to restrict prescription to specialists experienced in the treatment of osteoarthritis. Finally, information on the cutaneous risk in the SmPC was considered necessary.
- The PRAC concluded that the risk of severe diarrhoea associated with the use of diacerein containing medicinal products and the occurrence of potentially severe hepatic reactions could be mitigated by the above mentioned risk minimisation measures to be reflected in the SmPC and adequately monitored with yearly PSUR submissions.

The PRAC, as a consequence, concluded that the benefit-risk balance of the medicinal products containing diacerein identified in Annex I remains favourable, subject to the changes to the product information and conditions as provided for in Annex IV.

Appendix I

Divergent positions dated 6 March 2014

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

Diacerein containing medicinal products

Divergent position

Clinical trials and systematic reviews show at best, small beneficial effect of diacerein for treating symptoms of OA of the knee and hip (pain and physical functioning). Structure-modifying effects of cartilage by diacerein in OA have not been demonstrated, so its continuous use cannot be recommended beyond the control of symptoms of OA. Long-term efficacy is not certain and a sparing effect of diacerein on NSAIDs could not be confirmed.

The conclusions derived from most of the reviews are that the strength of evidence for effectiveness outcomes is low to moderate. It was confirmed that symptomatic benefit provided by diacerein in terms of pain reduction is minimal. The small benefit derived in terms of joint space narrowing is of questionable clinical relevance and was observed only for OA of the hip.

Two important safety issues have been identified to potentially impact the benefit-risk balance of diacerein: diarrhoea and hepatic reactions.

Diarrhoea is the most frequent GI effect. Even though MAHs claim most cases are non-severe and transient, some studies suggest that diarrhoea can be chronic (lasting > 4 weeks in up to 25% of diacerein treated patients). Therefore, it is considered that diarrhoea could be a major cause of disability that may lead to discontinuation of therapy and serious complications, particularly for elderly patients. The proposed risk minimisation measure for starting the treatment with half the regular daily dose (i.e., 50 mg/day) for the first 2 to 4 weeks is not adequate as half-dose may delay the time onset of diarrhoea and also preclude the efficacy of diacerein. Moreover, insufficient data is available to demonstrate beneficial effects of diacerein with this proposed dose.

OA population includes patients with concomitant regular use of hepatotoxic drugs, such as paracetamol or NSAIDs. As diacerein is an add-on therapy, the simple comparison of adverse events incidence between diacerein and NSAIDs/paracetamol is inadequate. Instead, one has to consider a potential additive or synergistic hepatotoxic effect of these drugs. Although we recognized that diacerein hepatotoxic effect is manifested mainly by mild/moderate increase of liver enzyme with a positive dechallenge, some rare serious cases were described. Additional follow-up measures such as regular monitoring of hepatic enzyme levels during the whole period of treatment could be required for monitoring this safety concern although the feasibility of such measure may be questioned.

Diacerein was proposed as an alternative treatment for patients who are intolerant or have contraindications to first line OA therapies, in particular to NSAIDs. However, diacerein is not indicated in substitution of paracetamol (gold standard for OA symptomatic treatment) or NSAIDs. Moreover, due to its delayed action diacerein is rather use as an add-on therapy, and comparisons should be restricted to the same class of OA treatments, that is, SYSADOAS. If a supplementary therapeutic is indicated in OA patients, other SYSADOAS alternatives may be safer (e.g. chondroitin sulphate, glucosamine).

Additionally, the risk minimisation activities presented by the MAHs did not provide any reassurance these would be effective regarding the reduction of risks, i.e.:

- the proposed measure to highlight the risk of diacerein-associated hepatotoxicity in the product labelling was not appropriate to reduce the risk of hepatotoxicity to an acceptable level, taking into account the suggested idiosyncratic mechanism of diacerein hepatotoxicity.
- the recommendation of reducing the posology at the start of the treatment to half a dose (50 mg once a day) for the first 2 to 4 weeks, and the recommendation that no laxatives should be used during diacerein treatment, were not appropriate to reduce the risk of severe diarrhoea to an acceptable level, taking into account the lack of data on the impact of a dose reduction with regards to the diminution of incidence and severity of diarrhoea.
- The proposal for limiting the use of diacerein to patients below 65 years to optimise the benefit-risk balance of diacerein is not evidenced by robust data.

The available data suggest that diacerein has a very modest effect on pain reduction, a questionable impact, if any, on function improvement and it is a lack of evidence of an NSAID sparing effect. In light of this and given the concerns that remain over the adequacy of the proposed risk minimisation to reduce the risks to an acceptable level, it is considered that the benefit/risk of diacerein containing products is negative.

PRAC member expressing a divergent position

Martin Huber (DE)	6 March 2014	Signature:
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Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

Diacerein containing medicinal products

Divergent position

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The available data suggest that diacerein has a very modest effect on pain reduction, a questionable impact, if any, on function improvement and it is a lack of evidence of an NSAID sparing effect. In light of this and given the concerns that remain over the adequacy of the proposed risk minimisation to reduce the risks to an acceptable level, it is considered that the benefit/risk of diacerein containing products is negative.

PRAC member expressing a divergent position

Margarida Guimarães (PT)		
	6 March 2014	Signature:

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

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Divergent position

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PRAC member expressing a divergent position

Jean-Michel Dogné (BE)	6 March 2014	Signature:
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Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

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PRAC member expressing a divergent position

Amy Tanti (MT)	6 March 2014	Signature:
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Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

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PRAC member expressing a divergent position

Julie Williams (UK)	6 March 2014	Signature:
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Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

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The available data suggest that diacerein has a very modest effect on pain reduction, a questionable impact, if any, on function improvement and it is a lack of evidence of an NSAID sparing effect. In light of this and given the concerns that remain over the adequacy of the proposed risk minimisation to reduce the risks to an acceptable level, it is considered that the benefit/risk of diacerein containing products is negative.

PRAC member expressing a divergent position

Menno van der Elst (NL)	6 March 2014	Signature:
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Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

Diacerein containing medicinal products

Divergent position

Clinical trials and systematic reviews show at best, small beneficial effect of diacerein for treating symptoms of OA of the knee and hip (pain and physical functioning). Structure-modifying effects of cartilage by diacerein in OA have not been demonstrated, so its continuous use cannot be recommended beyond the control of symptoms of OA. Long-term efficacy is not certain and a sparing effect of diacerein on NSAIDs could not be confirmed.

The conclusions derived from most of the reviews are that the strength of evidence for effectiveness outcomes is low to moderate. It was confirmed that symptomatic benefit provided by diacerein in terms of pain reduction is minimal. The small benefit derived in terms of joint space narrowing is of questionable clinical relevance and was observed only for OA of the hip.

Two important safety issues have been identified to potentially impact the benefit-risk balance of diacerein: diarrhoea and hepatic reactions.

Diarrhoea is the most frequent GI effect. Even though MAHs claim most cases are non-severe and transient, some studies suggest that diarrhoea can be chronic (lasting > 4 weeks in up to 25% of diacerein treated patients). Therefore, it is considered that diarrhoea could be a major cause of disability that may lead to discontinuation of therapy and serious complications, particularly for elderly patients. The proposed risk minimisation measure for starting the treatment with half the regular daily dose (i.e., 50 mg/day) for the first 2 to 4 weeks is not adequate as half-dose may delay the time onset of diarrhoea and also preclude the efficacy of diacerein. Moreover, insufficient data is available to demonstrate beneficial effects of diacerein with this proposed dose.

OA population includes patients with concomitant regular use of hepatotoxic drugs, such as paracetamol or NSAIDs. As diacerein is an add-on therapy, the simple comparison of adverse events incidence between diacerein and NSAIDs/paracetamol is inadequate. Instead, one has to consider a potential additive or synergistic hepatotoxic effect of these drugs. Although we recognized that diacerein hepatotoxic effect is manifested mainly by mild/moderate increase of liver enzyme with a positive dechallenge, some rare serious cases were described. Additional follow-up measures such as regular monitoring of hepatic enzyme levels during the whole period of treatment could be required for monitoring this safety concern although the feasibility of such measure may be questioned.

Diacerein was proposed as an alternative treatment for patients who are intolerant or have contraindications to first line OA therapies, in particular to NSAIDs. However, diacerein is not indicated in substitution of paracetamol (gold standard for OA symptomatic treatment) or NSAIDs. Moreover, due to its delayed action diacerein is rather use as an add-on therapy, and comparisons should be restricted to the same class of OA treatments, that is, SYSADOAS. If a supplementary therapeutic is indicated in OA patients, other SYSADOAS alternatives may be safer (e.g. chondroitin sulphate, glucosamine).

Additionally, the risk minimisation activities presented by the MAHs did not provide any reassurance these would be effective regarding the reduction of risks, i.e.:

- the proposed measure to highlight the risk of diacerein-associated hepatotoxicity in the product labelling was not appropriate to reduce the risk of hepatotoxicity to an acceptable level, taking into account the suggested idiosyncratic mechanism of diacerein hepatotoxicity.
- the recommendation of reducing the posology at the start of the treatment to half a dose (50 mg once a day) for the first 2 to 4 weeks, and the recommendation that no laxatives should be used during diacerein treatment, were not appropriate to reduce the risk of severe diarrhoea to an acceptable level, taking into account the lack of data on the impact of a dose reduction with regards to the diminution of incidence and severity of diarrhoea.
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The available data suggest that diacerein has a very modest effect on pain reduction, a questionable impact, if any, on function improvement and it is a lack of evidence of an NSAID sparing effect. In light of this and given the concerns that remain over the adequacy of the proposed risk minimisation to reduce the risks to an acceptable level, it is considered that the benefit/risk of diacerein containing products is negative.

PRAC member expressing a divergent position

Marieke De Bruin	6 March 2014	Signature:
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Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

Diacerein containing medicinal products

Divergent position

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The conclusions derived from most of the reviews are that the strength of evidence for effectiveness outcomes is low to moderate. It was confirmed that symptomatic benefit provided by diacerein in terms of pain reduction is minimal. The small benefit derived in terms of joint space narrowing is of questionable clinical relevance and was observed only for OA of the hip.

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PRAC member expressing a divergent position

Kirsti Villikka (FI)	6 March 2014	Signature:
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Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

Diacerein containing medicinal products

Divergent position

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PRAC member expressing a divergent position

Isabelle Robine (FR)	6 March 2014	Signature:
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Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

Diacerein containing medicinal products

Divergent position

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PRAC member expressing a divergent position

Doris Stenver (DK)	6 March 2014	Signature:
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Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1349

Diacerein containing medicinal products

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PRAC member expressing a divergent position

Carmela Macchiarulo (IT)	6 March 2014	Signature:
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